Dual Probes for the Dopamine Transporter and σ_1 Receptors: Novel Piperazinyl Alkyl-bis(4′-fluorophenyl)amine Analogues as Potential Cocaine-Abuse Therapeutic Agents

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Both dopamine uptake inhibitors and σ_1 receptor antagonists have been implicated as potential pharmacotherapeutics for the treatment of cocaine abuse. While the dopamine uptake inhibitors may share with cocaine neurochemical mechanisms underlying reinforcing properties, σ_1 antagonists have been shown to attenuate some behavioral actions and toxic side effects associated with cocaine overdose. Rimcazole, a σ_1 receptor antagonist that binds to the DAT (K_i = 224 nM), is not behaviorally cocaine-like and attenuates some of the behavioral actions of cocaine. To determine the roles of both DAT and σ_1 receptors in the behavioral actions of rimcazole, a series of analogues was synthesized. Initial studies identified two analogues (**1** and **4**) that showed high to moderate affinities for both DAT and σ_1 receptors and failed to show cocaine-like discriminative stimulus (DS) effects. A second series of bis(4′-fluorophenyl)-amine analogues have now been prepared in which the most potent DAT compound, **19** (K_i = 8.5 nM), was selective over serotonin transporter (SERT/DAT = 94), norepinephrine transporter (NET/DAT = 63), and σ_1 receptor binding (σ_1/DAT = 44). In addition, two other analogues **10** and **17** showed superior selectivity for DAT over SERT (170- and 140-fold, respectively) and DAT over NET (219- and 190-fold, respectively) but were essentially equipotent at DAT and σ_1 receptors (**10**; K_i = 77 and 124 nM, respectively, **17**; K_i = 28 and 13 nM, respectively). CoMFA studies at both DAT and σ_1 receptors were performed to examine structural requirements for optimal binding at these two targets as well as to assess differences between them. Behavioral evaluation of analogues with varying affinities for both DAT and σ_1 receptors may provide a novel approach toward designing medications for cocaine abuse.

Introduction

Identifying molecular mechanisms underlying the psychomotor stimulant and reinforcing effects of cocaine has provided direction in drug design toward the development of potential cocaine-abuse medications. An ideal medication would target mechanism(s) most likely responsible for cocaine's actions, and might, in turn, reduce drug seeking and ultimately normalize physiological and neurochemical function that has been disrupted by chronic cocaine abuse (for review, see ref 1). As substantial literature has established that the mesolimbic dopamine system is the primary mechanistic target for the reinforcing effects of cocaine, medication development has been primarily directed toward dopamine uptake inhibitors (indirect dopamine agonists) and full or partial dopamine receptor agonists.[2,3] Other neurochemical systems that may be able to modulate the dopaminergic system through indirect actions, such as σ_1 receptor antagonists, have also been explored, although to a lesser degree (for review, see refs 1−4). The latter mechanism has been featured in several recent reports wherein σ_1 receptor antagonists have been reported to block cocaine-induced conditioned place preference.[5,6] Subsequently, the development of σ_1 antagonists has been proposed as a strategy toward cocaine-abuse medication development.[4]

Rimcazole, a moderately potent σ_1 antagonist,[7] has been reported to attenuate the locomotor stimulatory effects produced by acute and subchronic administration of cocaine.[8,9] Rimcazole also protects against cocaine-induced convulsions, but not lethality, as other more selective σ_1 antagonists have been reported to do.[9] Rimcazole binds equipotently to cocaine at the dopamine transporter (DAT) which is ∼4-fold higher than its binding affinity at σ_1 receptors.[10,11] These studies prompted the design, synthesis, and evaluation of a series of rimcazole analogues as tools to further elucidate the roles both DAT and σ_1 receptors play in the pharmacological actions of these agents (Figure 1).

Rimcazole bears structural similarities to the potent dopamine uptake inhibitor, GBR 12909, which has well-described structure−activity relationships at both the dopamine transporter and σ receptors.[3,12−16] In our initial series of rimcazole analogues, the most potent DAT inhibitor, **1** (K_i = 61 nM), showed moderately

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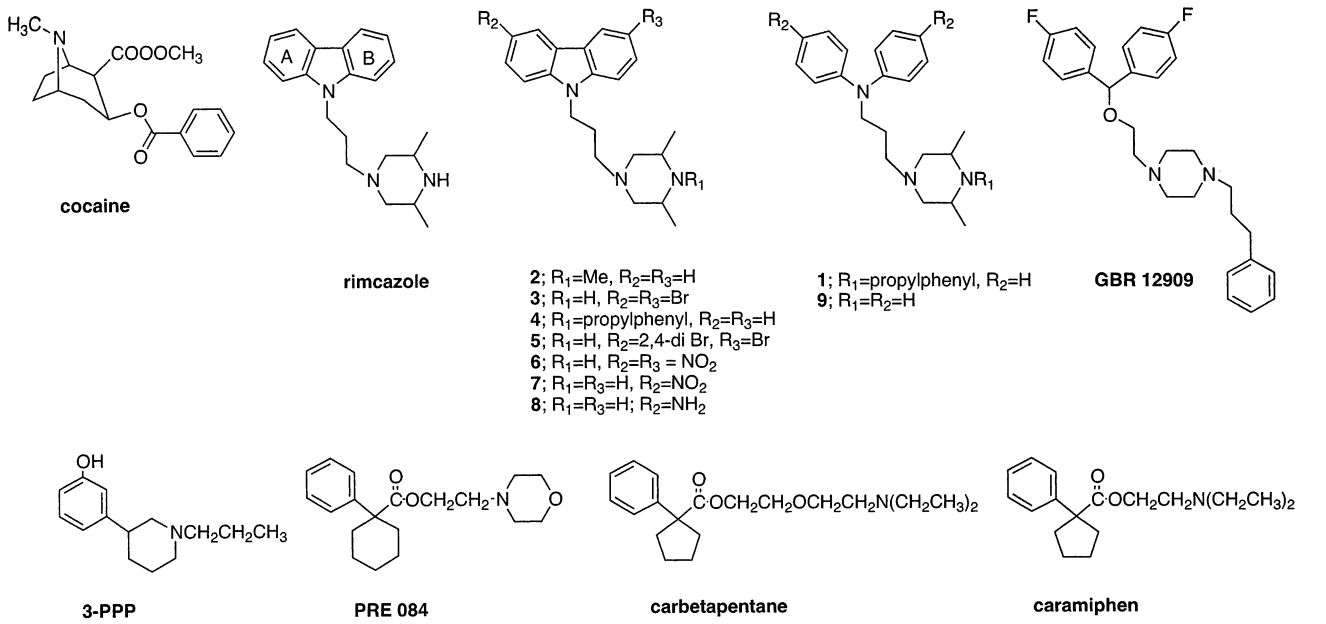


Figure 1. Chemical structures of previously reported DAT/σ_1 ligands.

potent σ_1 binding affinity (K_i = 97 nM) and was ~3-fold less potent at SERT (K_i = 219 nM) and 60-fold selective over NET.[11] Several rimcazole analogues (**1**−**4**) were evaluated in animal models of cocaine abuse and toxicity.[9,17] None of these compounds, like the parent rimcazole, demonstrated a cocaine-like behavioral profile. Some attenuated several behavioral effects of cocaine and protected against cocaine-induced seizures in rats.[9,17] On the basis of these results, we hypothesized that despite their actions at DAT, perhaps σ_1 receptor antagonism was playing a role in the behavioral actions of rimcazole and its analogues. Furthermore, the idea that DAT mediated cocaine-like actions, including reinforcement, might be modulated by σ_1,[4] supported the design of dual DAT/σ_1 probes to further investigate whether these combined actions might provide a novel approach to cocaine-abuse medication discovery.

A second generation of analogues was thus designed in an attempt to either (1) maximize DAT selectivity over SERT and NET, while retaining σ_1 receptor binding or (2) synthesize potent and selective DAT ligands with reduced σ_1 actions to further define the individual roles of DAT and σ_1 receptors in this series of molecules. Results from previous SAR studies suggested that substitution of the carbazole ring system of rimcazole with bis(4′-fluorophenyl)amine and substituting the terminal piperazine nitrogen with a propylphenyl moiety might improve binding affinity and selectivity for the DAT.[11,18] A second series of compounds was designed wherein the methyl groups in positions 2 and 6 of the piperazine ring were removed and a hydroxyl group was placed on the linking alkyl chain, in one compound, in an attempt to retain high affinity binding at DAT and reduce lipophilicity.

Chemistry

The synthesis of novel analogues **10**−**13** have been previously described.[18] Synthetic details that were not published for these compounds are included in the Experimental Section. In Scheme 1, coupling of **14**[18] with piperazine followed by reduction with LAH gave compound **15** in 39%, over two steps. Compounds **16** and **17** were prepared in a similar manner with their respective alkylating agent. Compound **15** was reacted with 3-chloropropiophenone in acetone to give ketone **18** as a yellow oil. Reduction of **18** with LAH gave the racemic product **19** in 74% yield, over two steps. All final products were crystallized as their HCl or HBr salts. The structure of compound **11** was elucidated by X-ray crystallography as shown in Figure 2.

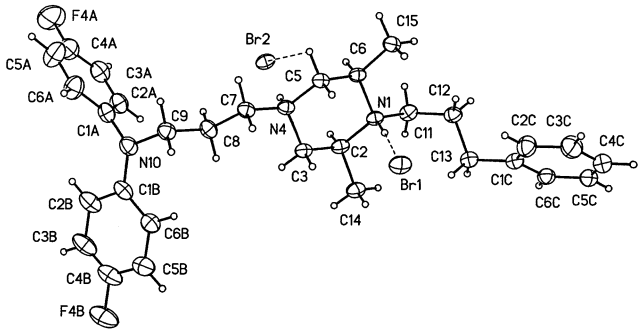
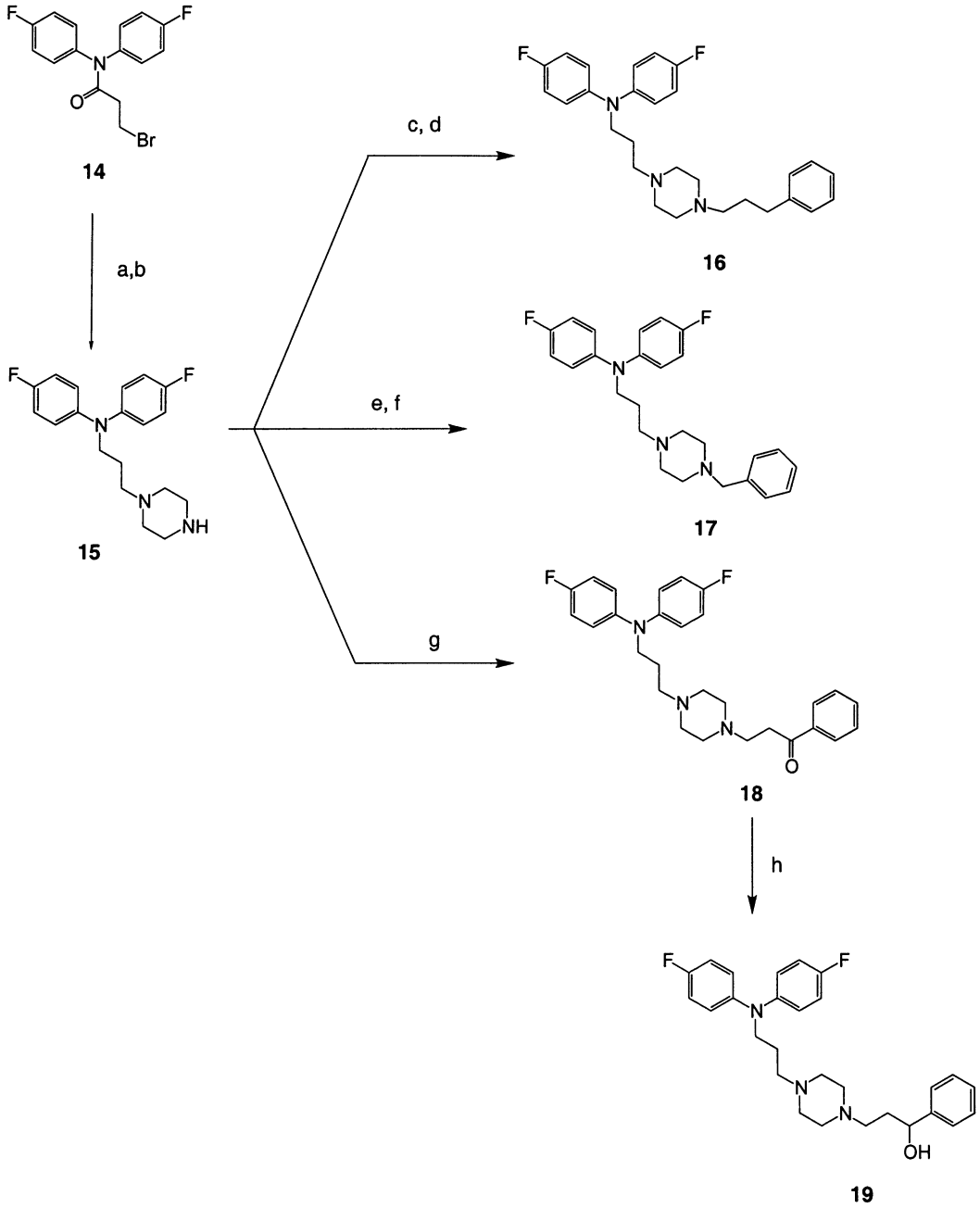


Figure 2. The molecular structure and numbering scheme for compound **11** with displacement ellipsoids drawn at the 30% probability level.

Structure−**Activity Relationships.** All novel rimcazole analogues were evaluated for displacement of radioligands from DAT ([^{3}H]WIN 35,428) and SERT ([^{3}H]citalopram) in rat brain. Note that [^{3}H]citalopram is a different radioligand than previously reported,[11] and thus the SERT binding affinities for compounds **1** and **9** differ from those in our earlier report. Binding at NET ([^{3}H]nisoxetine) was also evaluated in rat brain and ratios of the respective K_i values as compared to DAT provided the selectivity indices found in Table 1.

For optimal binding affinity at DAT, the diphenylamine was substituted with 4′-F groups, and the terminal piperazine nitrogen was substituted with *n*-propylphenyl (**11** and **16**). Removal of the 2,6-dimethyl groups had no effect on DAT binding but served to decrease lipophilicity, as seen by a comparison of cLogD

Scheme 1[a]

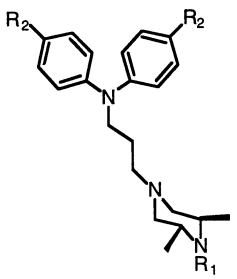


[a] Reagents and conditions: (a) piperazine, DMF, H_2O, K_2CO_3, 80 °C, 2 h; (b) LAH, THF, reflux, 2 h; (c) hydrocinnamic acid, $SOCl_2$, toluene, reflux, overnight; (d) LAH, THF, reflux, 2 h; (e) benzoyl chloride, toluene, reflux, overnight; (f) LAH, THF, reflux, 2 h; (g) 3-chloropropiophenone, acetone, rt, 12−16 h; (h) LAH, THF, reflux, 2 h.

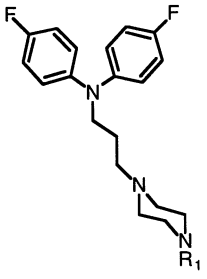
(calculated partition coefficient at physiological pH 7.4; ACD/LogD Suite, Advanced Chemistry Development Inc., Toronto, Canada) values wherein **11** cLogD = 6.94 and **16** cLogD = 6.03 (Table 2). Addition of a hydroxyl group on the terminal *N*-propylphenyl chain resulted in the most potent DAT ligand in the series (**19**; K_i = 8.5 nM) with significantly reduced lipophilicity (cLogD = 4.81). This substitution has also been successful in the GBR series of compounds[19,20] and may provide a point of departure for additional chemical modification. In addition, as compared to GBR 12909, compound **19** is significantly more selective for DAT over SERT (9-fold v. 94-fold, respectively) and remains selective over NET (63-fold). These SARs are comparable to those reported in the piperazine and piperidine series of GBR 12909 analogues at DAT.[12−16]

Significant selectivity for DAT over NET was achieved with the *N*-ethyl-3,4-dichlorophenyl substituent of compounds **12** and **13** (>560-fold and >110-fold selective, respectively). However, the addition of this terminal N-substituent decreased DAT binding affinity and significantly increased lipophilicity with **12** having a cLogD value of 7.56. The most overall DAT versus SERT and NET selective compounds in this series were **10** and **17**. However, neither of these compounds exhibited selectivity over σ_1 binding (σ_1/DAT = 1.5 and 0.5, respectively). In fact, most of the analogues were not DAT over σ_1-selective, with **19** being the single exception

Table 1. Binding Results at the Monoamine Transporters



A

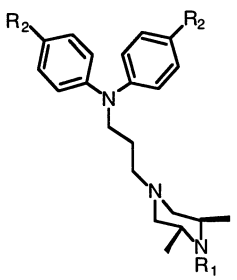


B

compd	R_1, R_2	[^{3}H]WIN 35,428 (DAT) K_i (nM)[a]	[^{3}H]citalopram (SERT) K_i (nM)[a]	[^{3}H]nisoxetine (NET) K_i (nM)[a]	SERT/DAT	NET/DAT
1	A, propylphenyl, H	61.0 ± 6.1[b]	1220 ± 160[c]	3640 ± 440[b]	20	60
9	A, H, H	813 ± 22[b]	70 900 ± 6600[c]	6810 ± 600[b]	87	8
10	A, H, F	77.1 ± 5.0	13 100 ± 1800[c]	16900 ± 990[c]	170	219
11	A, propylphenyl, F	22.8 ± 2.0	2130 ± 160[c]	1020 ± 140[c]	94	45
12	A, 3,4-diCl-phenethyl, F	180 ± 16	4350 ± 260[c]	>100 000[c]	24	>560
13	A, 3,4-diCl-phenethyl, H	272 ± 6.5	5010 ± 580[c]	>30 000[c]	18	>110
15	B, H	60.8 ± 9.0	133 ± 16	396 ± 32	2	7
16	B, propylphenyl	18.1 ± 2.7	1210 ± 6.2	682 ± 97	67	38
17	B, benzyl	27.6 ± 3.9	3730 ± 440	5210 ± 590	140	190
19	B, 3-OH-propylphenyl	8.5 ± 0.8	803 ± 99	532 ± 38	94	63
rimcazole	–	224 ± 16[c]	1710 ± 72	2160 ± 300[b]	8	10
GBR 12909	–	11.9 ± 1.9[c]	105 ± 1.0	1270 ± 190	9	106

[a] The binding methods used are as reported in ref 29, and K_i values were analyzed using PRISM. [b] Data from ref 11. [c] Data from ref 18.

Table 2. Binding Results at the DAT and σ Receptors



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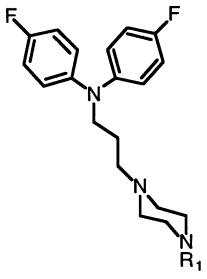

B

compd	R_1, R_2	[^{3}H]pentazocine (σ_1)[a]	[^{3}H]DTG/dextrallorphan (σ_2)[a]	σ_1/DAT	cLogD values[b]
10	A, F, H	124.0 ± 11	NT	1.6	3.23
11	A, F, propylphenyl	11.1 ± 0.8	18.6 ± 1.9	0.5	6.94
12	A, F, 3,4-diCl-phenethyl	32.5 ± 3.6	1170 ± 22	0.2	7.56
13	A, H, 3,4-diCl-phenethyl	29.6 ± 2.7	216 ± 20	0.1	6.84
15	B, H	1390 ± 98	385 ± 46	23	2.36
16	B, propylphenyl	66.2 ± 3.6	NT	3.7	6.03
17	B, benzyl	13.1 ± 1.2	78.1 ± 9.2	0.5	5.14
19	B, 3-OH-propylphenyl	372 ± 21	NT	44	4.81

[a] The binding methods used are as reported in ref 11. [b] cLogD values calculated from the ACD/Log*D* Suite, Advanced Chemistry Development Inc., Toronto, Canada.

with a σ_1/DAT = 44 (Table 2). Note that this is a similar σ_1/DAT ratio to cocaine (σ_1/DAT = 47, Table 3). Thus, most of these compounds had binding affinities for σ_1 in the range of their DAT binding affinities. For those compounds that were evaluated for σ_2 binding, most showed no σ_2 selectivity, although compound **11** was equiactive at σ_1, σ_2, and DAT and **15** was 3.6-fold σ_2 selective. It is unclear, at this time if σ_2 receptors play any role in the pharmacological actions of this series of compounds or cocaine.

Molecular Modeling. Several CoMFA models were derived, and the best results are summarized in Table 4. For Alignment I, DAT binding affinities of the entire data set were used and yielded a cross-validated correlation of 0.334 using three components and a conventional r^2 of 0.868. Earlier a study was performed wherein the column filter value (σ value), which defines the signal-to-noise ratio, was varied from (2.0, 1.0 and 0.5), and a value of 1.0 kcal/mol provided a more correlative and predictive model. Hence, all further studies were performed using 1.0 kcal/mol as the column filter value. Analysis of the residuals of the compounds showed that compounds **6** and **7** were poorly predicted; however, compound **7** had high residuals. After elimination of compound **7** a cross-validated r^2 value of 0.709 and a non-cross-validated r^2 of 0.977 was obtained. The relative contributions to the CoMFA models were approximately 35% steric and 65% electrostatic interactions, for this series of compounds. A plot of actual versus predicted activities of the compounds is depicted

Table 3. Binding Results at the DAT and σ_1 Receptors

compd	[^{3}H]WIN 35,428 (DAT), K_i (nM)	[^{3}H]pentazocine (σ_1), K_i (nM)[a]	CLogD[d]	σ_1/DAT
1	61.0 ± 6.1[b]	97.2 ± 14.0[b]	6.22	1.6
2	436 ± 44[b]	552 ± 110[b]		1.3
3	3890 ± 500[b]	4420 ± 27[b]		1.1
4	263 ± 34[b]	104 ± 0.4[b]		0.4
5	30 300 ± 2400[b]	–		–
6	174 000 ± 24000[b]	–		–
7	109 ± 7[b]	596 ± 66[b]		5.5
8	2400 ± 140[b]	5720 ± 440[b]		2.4
9	813 ± 22[b]	138 ± 2.0[b]		0.2
rimcazole	224 ± 16[b]	908 ± 99[b]	2.88	4.1
S-(−)-3-PPP	3270 ± 200[c]	234 ± 6.3		0.07
PRE 084	5340 ± 590[c]	46.5 ± 3.9		0.009
caramiphen	5180 ± 310[c]	15.5 ± 0.7		0.003
carbetapentane	3090 ± 190[c]	19.5 ± 0.06		0.006
GBR 12909	11.9 ± 1.9[b]	318 ± 18[b]	5.97	27
cocaine	187 ± 19[b]	8830 ± 860	1.51	47

[a] The binding methods used are as reported in ref 11. [b] Data from ref 11. [c] Data from ref 10. [d] cLogD values calculated from ACD/Log*D* Suite, Advanced Chemistry Development Inc., Toronto, Canada.

Table 4. Summary of CoMFA Results

	Alignment I		Alignment II	
	DAT	σ_1	DAT	σ_1
r^2_{cv}	0.709	0.460	0.673	0.521
components	4	3	4	4
SEP	0.699	0.630	0.741	0.613
r^2_{ncv}	0.977	0.892	0.971	0.929
SEE	0.194	0.281	0.222	0.236
F	184.467	44.147	140.766	49.274
steric	35.5	50.8	37.8	51.7
electrostatic	64.5	49.2	62.2	48.3

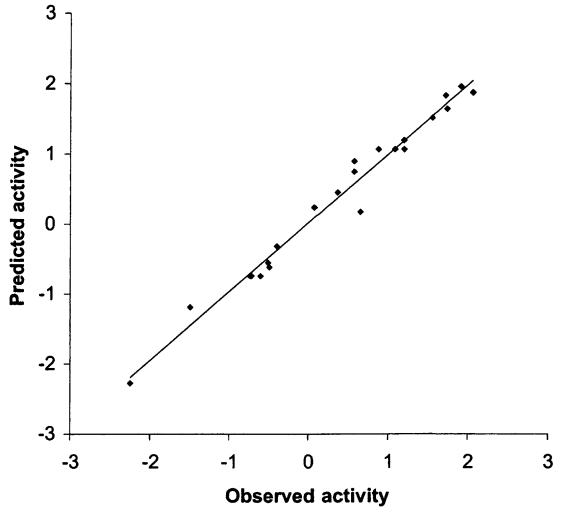

Figure 3. Plot of observed vs predicted activity for DAT model from Alignment I.

in Figure 3. Several CoMFA models were derived from the entire data set (including **7**), wherein the traditional CoMFA descriptors were supplemented with additional descriptors; however, there was no improvement in the CoMFA results. Compounds **6** and **7** contain a strong electron-withdrawing nitro group on the diaryl ring system. There was a 1600-fold decrease in DAT affinity for compound **6** as compared to compound **7**. The moderate affinity of compound **7** is less represented in the dataset, leading to its underprediction. Compound **6** was well predicted as less active at the DAT by this CoMFA model after eliminating compound **7**.

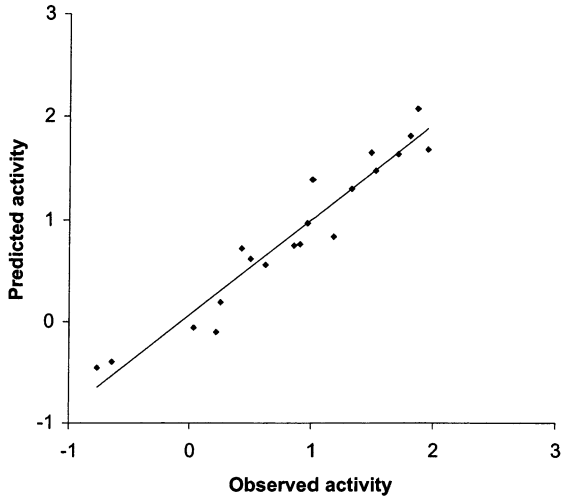

Figure 4. Plot of observed vs predicted activity for σ_1 receptor model from Alignment II.

When Alignment I was used to correlate the CoMFA descriptors with σ_1 receptor activity, it showed a cross-validated r^2 of 0.247 and non-cross-validated r^2 of 0.765. In this model, **15** was a poorly predicted compound and was excluded from a second CoMFA model, which showed an improved cross-validated r^2 of 0.460 with three components and a non-cross-validated r^2 of 0.892. This CoMFA model showed almost equal contributions from steric and electrostatic fields. Alignment of the compounds using the Na nitrogen (Alignment II) showed a decreased cross-validated r^2 of 0.673 and a non-cross-validated r^2 of 0.971 for DAT affinities. However there was an increase in the correlative properties for CoMFA models derived using σ_1 receptor activity. This σ_1 receptor CoMFA model showed a cross-validated r^2 of 0.521 and a non-cross-validated r^2 of 0.929. Thus alignment of the Na nitrogen is essential for σ_1 activity. Figure 4 shows the plot of actual versus predicted activities of compounds derived from this model.

The CoMFA contour maps were generated by interpolating the products between the 3D-QSAR coefficients and their associated standard deviations. Figure 5 shows the steric and electrostatic contour maps derived from the activity at DAT. The green and yellow polyhedra describe regions where increase in steric bulk increases or decreases the activity, respectively. A large sterically favored region was observed near the Nb (terminal nitrogen) substituent. Many compounds in this series have shown improved activity upon substitution of the bulky group at the Nb nitrogen. There was an increase in DAT binding as the size of the Nb substituent was increased, as seen in compounds **15** compared to **16**. There was a large sterically unfavored yellow region around the diarylamine substituent. This defines a limiting binding site, as an increase in steric bulk in this region reduces the activity. For example, **3** and **6** had substituents which overlapped in this region, thus reducing their affinities toward DAT. The steric regions define the size and shape of the substituents around the molecule, but it is the electrostatic contribution that overrides the steric interactions to the binding site. A large positive charge favoring blue region was observed near the diaryl substituent, suggesting electron-withdrawing groups on the aromatic rings would be favorable for activity, explaining the low activity for

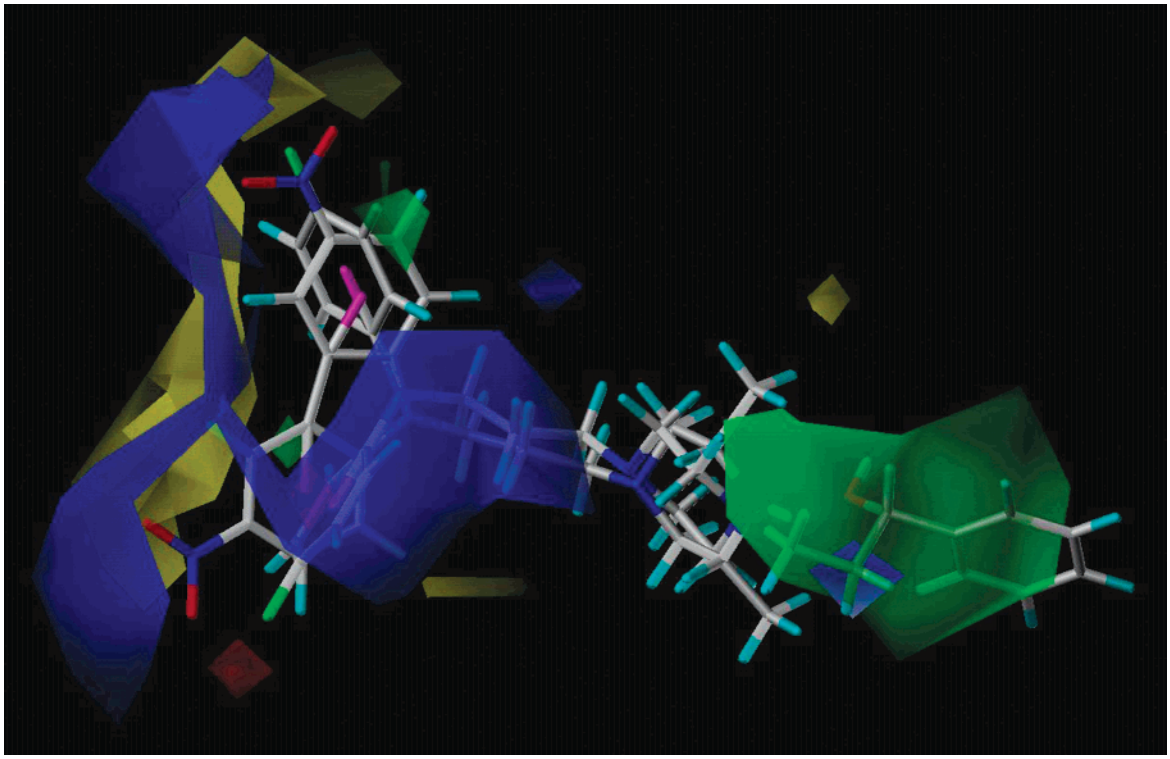

Figure 5. The CoMFA contour graphs for the activity on DAT obtained from the PLS analysis of the Alignment I. The sterically favored and unfavored (contribution at 80% and 20%) are shown as green and yellow fields, respectively, and positive charge favorable and unfavorable (contribution at 80% and 20%) are shown as blue and red fields, respectively. The highly active compound **19** and less active compound **6** are shown for comparison.

compound **8**, which contained an amino group in this blue region. However, this blue region overlaps the sterically unfavored yellow region, suggesting that a small electron-withdrawing substituent is required. This is illustrated by the less active compound **6**, where the electron-withdrawing nitro group overlaps in the yellow region, and improvement in the activity for compound **10** compared to **9**, because of substitution of the *p*-F group.

Figure 6 shows the steric and electrostatic contour maps derived using σ_1 activity. The CoMFA contours were more scattered than those for the DAT model. A sterically favored green region was observed near the Nb substituent, suggesting that a strong steric interaction in this region of the molecule, as indicated by increases in activity for *N*-propylphenyl-substituted compounds **1** and **4** over **9** and rimcazole, respectively. Also the scattered yellow regions around the molecule define the limits for size and shape of the substituents. Positive charge-favoring regions depicted as blue contours were observed in the vicinity of the para-position of the diaryl ring system. Hence small electron-withdrawing substituents are predicted to improve the binding affinities as indicated by an increase in activity for compounds **9** and **10** compared to **1** and **11**, respectively.

Putative binding site characteristics for the σ_1 receptor have been proposed.[21−24] The CoMFA results reported herein can be interpreted in light of these models, and the binding features of the rimcazole analogues are comparable. The distance between the nitrogen Na and centroid of the terminal phenyl ring (hydrophobic site) was 8.28 Å, equivalent to the optimum distance of 8.3 Å proposed in one model.[22] A similar comparison of the distances for a template compound with the proposed model suggested that these compounds could be binding as phenylpiperazines and phenylpiperidines.[22,25] As such, the substituent on the Nb nitrogen of the rimcazole analogues could be binding in the primary hydrophobic site, and the diarylamine could be accessing the secondary binding site, which seems to tolerate bulk in this region. The region between the Nb nitrogen and the terminal phenyl ring is less tolerant to electron-releasing or hydrophilic substituents as the 3-OH group of compound **19** overlaps in the blue contour, which is unfavorable for activity. Likewise, comparison with the proposed σ receptor model[22] would suggest that hydrophilic interactions in this region would reduce affinity toward the σ_1 receptor.

The commonalities of the occurrence of the fields around the molecules provide potential avenues for modifying these ligands as dual probes for DAT and σ_1 activity. The substituent at the Nb nitrogen is essential for activity at the σ receptor, as shown by increases in σ_1 affinity of **4** over rimcazole, whereas there was no major effect on the DAT binding affinity (Table 3). The σ_1 receptor tolerates larger nonplanar substituents in the diaryl substituent region, whereas it is detrimental for DAT (rimcazole compared to **9**); however, in such compounds there was improvement (>10-fold) in the DAT binding affinity after substitution at the Nb nitrogen (**1** compared to **9**). Similarly, there was an increase in σ_1 binding affinity for compounds **11** and **16** over compounds **10** and **15**, respectively, by 10−20-fold. Therefore for optimal DAT binding, properly substituted diaryl groups with an amino group for ionic interactions are sufficient, whereas for σ_1 receptor the hydrophobic substituent at the Nb nitrogen is essential. The *p*-

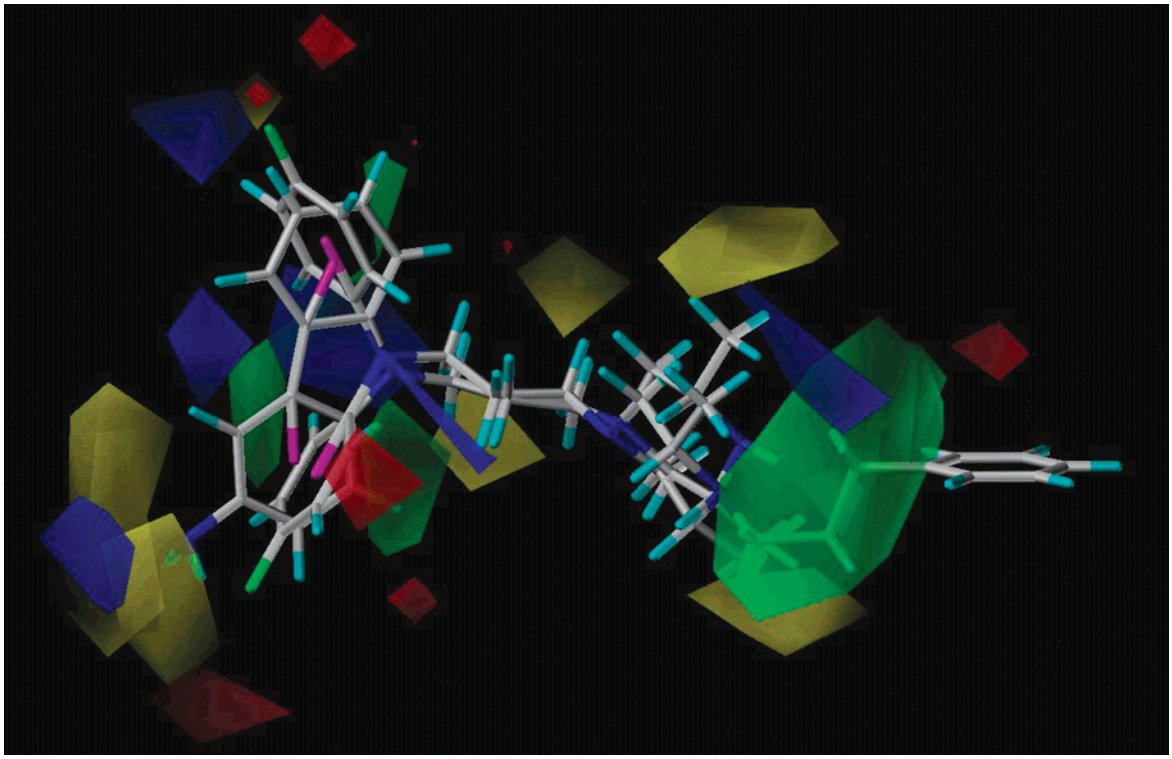

Figure 6. The CoMFA contour graphs for the activity on the σ_1 receptor obtained from the PLS analysis of the Alignment II. The sterically favored and unfavored (contribution at 80% and 20%) are shown as green and yellow fields, respectively, and positive charge favorable and unfavorable (contribution at 80% and 20%) are shown as blue and red fields, respectively. The highly active compound **12** and less active compound **8** are shown for comparison.

difluoro groups are favorable for the activity at both targets; however, there was a more profound increase in DAT binding affinity (**10** compared to **9**) than at σ_1 receptors.

Summary

In summary, a continuation of our efforts to synthesize analogues of rimcazole that have high affinity for DAT and σ_1 receptors is described. Many of these compounds were selective for DAT over SERT and NET with **10** and **17** demonstrating particularly good selectivity. One analogue, **19**, demonstrated the highest DAT affinity in this series with moderate selectivity over SERT, NET, and σ_1 receptors. CoMFA models were derived for activity at both DAT and σ_1 receptors. The comparison of the distances for a template molecule with previously proposed σ receptor models[22,24] showed significant compatibility, suggesting that these rimcazole analogues likely bind using the described pharmacophoric features. The σ_1 receptor model showed common features with the DAT model, providing sites where ligands could be modified to develop and optimize the activity at both targets.

Reducing the lipophilicity in this series of analogues is anticipated to aid in in vivo experiments, which are often hampered by hydrophobic and insoluble drugs. By removing the 2,6-dimethyl substituents on the piperazine ring, high affinity ligands at both DAT and σ_1, with lower lipophilicity than previously reported analogues, were obtained. Further reduction in lipophilicity was also achieved by placing a hydroxyl group on the terminal *N*-propylphenyl chain (**19**). Behavioral evaluation of **10**, **11**, and **19** is currently underway in animal models of cocaine abuse to assess if these compounds display cocaine-like actions and how they effect cocaine's actions, in these models. These studies will provide further insight on the roles DAT and σ_1 receptors play in cocaine-like behaviors and whether dual action DAT/σ_1 targeting might be a reasonable approach for future drug development.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Billerica, MA) AC-300 instrument. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$ or D_2O). Proton and carbon chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (Me_4Si; 0.00 ppm) which was used as an internal standard. Mass spectra were recorded on a Hewlett-Packard (Palo Alto, CA) HP 6890 Series. Infrared spectra were recorded as a neat film on KBr plates with a Perkin-Elmer RX FT-IR. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within ±0.4% of calculated values. All flash column chromatography was performed using the flash-grade silica gel (Aldrich, 230−400 mesh, 60 Å). All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc. unless otherwise indicated and used without further purification.

Chemistry. 3-Bromo-*N*,*N*-bis(4-fluorophenyl)propanamide (14). 3-Bromopropanoyl chloride (4.34 g, 25 mmol) was added to a solution of *N*,*N*-bis(4-fluorophenyl)amine[26] (5 g, 24 mmol) in benzene (25 mL) and stirred at reflux for 5 h under argon. The solvent was removed, and the residue was purified by flash column chromatography [eluting with toluene followed by hexane/ethyl acetate (5:1)] to give a white solid (6.9 g, 83%): mp 96−97 °C; IR ($CHCl_3$) 1660 (CO) cm^{-1} ; ^{1}H NMR δ 2.82 (2H, t, J = 6.6 Hz), 3.65 (2H, t, J = 6.6 Hz), 6.92−7.26 (8H, m, aryl-Hs); MS(EI) 339 (M^+).

[3-(*cis*-3, 5-Dimethyl-1-piperazinyl)propyl]-*N*,*N*-bis(4-fluorophenyl)amine Hydrochloride (10). 2,6-Dimethylpiperazine (1.17 g, 10 mmol) was added to a solution of **14** (1.17

g, 10 mmol) in DMF (85 mL) and H_2O (4.16 mL), followed by addition of K_2CO_3 (5.53 g, 40.5 mmol). The solution was warmed to 80 °C for 2 h. The mixture was filtered, and the filtrate was concentrated in vacuo, dissolved in H_2O (100 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), and evaporated to give the crude product. Purification by flash column chromatography (3% $CHCl_3$/MeOH/NH_4OH) gave the pure amide (3.77 g, 100%) as a yellow oil; IR ($CHCl_3$) 1673 (CO) cm^{-1}. The intermediate amide was dissolved in THF (30.8 mL) and added dropwise to a mixture of LAH (0.79 g, 20.8 mmol) in THF (6.21 mL) at 0 °C and stirred overnight at rt. The mixture was quenched with H_2O (0.9 mL), 15% NaOH (0.9 mL), and H_2O (2.7 mL) successively, at 0 °C. The reaction mixture was filtered, washed with THF, and evaporated to dryness, to give the crude product, which was purified by flash column chromatography (3% $CHCl_3$/MeOH/NH_4OH) to give the product as a light yellow oil (2.8 g, 77%). The HCl salt was made by dissolving the free base in methanolic HCl and was recrystallized from MeOH/ether; mp 234−236 °C (dec); ^{1}H NMR δ 1.04 (6H, d, 2 × CH_3), 1.55 (2H, t, J = 11 Hz), 1.78 (2H, t, J = 7.0 Hz), 2.33 (2H, t, J = 7.0 Hz), 2.72−2.92 (4H, m), 3.66 (2H, t, J = 7.1 Hz, $CH_2N(PhF)_2$), 6.92−6.95 (8H, m, aryl-Hs); ^{13}C NMR δ 20.3, 25.0, 50.9, 51.1, 56.0, 61.1, 116.1, 116.4, 122.6, 122.7, 145.0, 156.7, 159.8, 168.1; MS(EI) 359 (M^+); Anal. ($C_{21}H_{27}F_2N_3$·2HCl), C, H, N.

[3-(*cis*-3,5-Dimethyl-4-[3-phenylpropyl]-1-piperazinyl)-propyl]-*N*,*N*-bis(4-fluorophenyl)amine Hydrobromide (11). Hydrocinnamic acid (1.84 g, 12.42 mmol) was dissolved in thionyl chloride (32 mL, 463 mmol), and the solution was warmed to 50 °C and stirred for 90 min. The excess thionyl chloride was removed by distillation. The residue was taken up in toluene (35 mL) and added to a solution of **10** (2.7 g, 7.5 mmol) in toluene (35 mL). The reaction mixture was stirred at reflux overnight, then extracted with 20% Na_2CO_3 (3 × 50 mL), washed with brine (50 mL), and dried (Na_2SO_4). Removal of the volatiles gave the crude product, which was purified by flash column chromatography (3% $CHCl_3$/MeOH/NH_4OH) to yield the amide intermediate (3.5 g, 95%) as a yellow oil. The intermediate amide (3.5 g, 7.13 mmol) was dissolved in THF (21.47 mL) and added dropwise to a mixture of LAH (0.541 g, 14.26 mmol) in THF (4.33 mL) at 0 °C and stirred overnight at rt. The mixture was quenched with H_2O (0.6 mL), 15% NaOH (0.6 mL), and H_2O (1.8 mL) successively, at 0 °C. The reaction mixture was filtered and washed with THF and evaporated to dryness. The crude product was purified by flash column chromatography (2% $CHCl_3$/MeOH/NH_4OH) to give the product as a light yellow oil (2.5 g, 74%). The HBr salt was made by dissolving the free base in methanolic HBr and then recrystallizing from acetone/ether; mp 229.5−230.5 °C; ^{1}H NMR δ 0.98 (6H, d, J = 5.9 Hz, 2 × CH_3), 1.22−1.25 (2H, m), 1.58−1.80 (4H, m), 2.25−2.29 (2H,m), 2.51−2.54 (2H,m), 2.56−2.68 (4H,m), 2.78 (2H, t, J = 7.9 Hz, CH_2Ph), 3.64 (2H, t, J = 7.1 Hz, $CH_2N(PhF)_2$), 6.92−7.36 (13H, m, aryl-Hs); ^{13}C NMR δ 18.0, 24.6, 33.8, 47.5, 50.7, 53.5, 55.3, 61.4, 115.7, 116.0, 122.2, 122.3, 125.8, 128.3, 128.4; MS(EI) 477 (M^+), 218 ($^+CH_2N(PhF)_2$); Anal. ($C_{30}H_{37}F_2N_3$·2HBr·H_2O), C, H, N.

[3-(*cis*-3,5-Dimethyl-4-[2-(3,4-dichlorophenyl)ethyl]-1-piperazinyl)propyl]-*N*,*N*-bis(4-fluorophenyl)amine hydrochloride (**12**) was prepared as described for **11** from **10** (0.59 g, 1.64 mmol) using 3,4-dichlorophenylacetic acid (0.56 g, 2.71 mmol). After coupling and reduction (0.6 g, 69% from **15**), the amine was converted to the HCl salt. The product was recrystallized from acetone/ether; mp 211−213 °C (dec) ^{1}H NMR δ 1.12 (6H, d, J = 6.0 Hz, 2 × CH_3), 1.61−1.85 (4H, m), 2.31 (2H, t, J = 7.1 Hz), 2.61−2.77 (6H, m), 2.92−2.98 (2H, m), 3.66 (2H, t, J = 7.2 Hz, $CH_2N(PhF)_2$), 6.88−7.00 (7H, m, aryl-Hs), 7.25 (2H, d, J = 9.06 Hz, aryl-Hs), 7.35 (2H,d, J = 8.2 Hz, aryl-Hs); ^{13}C NMR δ 18.1, 24.7, 29.1, 49.8, 50.7, 53.5, 55.3, 61.3, 115.8, 116.1, 122.3, 122.4, 128.0, 130.4, 130.5, 144.6; MS(EI) 531 (M^+), 218 ($^+CH_2N(PhF)_2$); Anal. ($C_{29}H_{33}F_2N_3Cl_2$·2HCl·H_2O), C, H, N.

[3-(*cis*-3,5-Dimethyl-4-[2-(3,4-dichlorophenyl)ethyl]-1-piperazinyl)propyl]diphenylamine hydrochloride (**13**) was prepared as in **12** from [3-(*cis*-3,5-dimethyl-1-piperazinyl)-propyl]diphenylamine[11] (0.53 g, 1.64 mmol) and 3,4-dichlorophenylacetic acid (0.56 g, 2.71 mmol). After coupling and reduction (0.43 g, 53%), the amine was converted to the HCl salt and was recrystallized from acetone; mp 221−224 °C; ^{1}H NMR δ 1.11 (6H, d, J = 6.1 Hz, 2 × CH_3), 1.64−1.88 (4H, m), 2.32 (2H, t, J = 7.2 Hz), 2.61−2.78 (6H, m), 2.92−2.98 (2H, m), 3.75 (2H, t, J = 7.3 Hz, $CH_2N(PhF)_2$), 6.91−7.36 (13H, m, aryl-Hs); ^{13}C NMR δ 18.0, 24.5, 28.8, 49.6, 50.0, 53.3, 55.2, 61.2, 120.8, 121.0, 127.9, 129.1, 130.3, 130.4, 140.8, 147.9; MS-(EI) 495 (M^+); Anal. ($C_{29}H_{35}N_3Cl_2$·2HCl·0.5H_2O), C, H, N.

[3-(1-Piperazinyl)propyl]-*N*,*N*-bis(4-fluorophenyl)-amine hydrochloride (**15**) was prepared as described for **10** from **14** (5.2 g, 15.3 mmol), using piperazine (1.32 g, 15.3 mmol). After coupling and reduction (1.96 g, 39% from **14**), the amine was converted to the HCl salt and recrystallized from acetone/ether; mp 216−218 °C (dec) ^{1}H NMR δ 1.72−1.80 (2H, m CH_2), 2.17−2.37 (4H, m), 2.86−2.89 (6H, m), 3.67 (2H, t, J = 7.2 Hz, $CH_2N(PhF)_2$), 6.92−7.00 (8H, m, aryl-Hs); ^{13}C NMR δ 24.9, 25.1, 46.4, 51.0, 55.0, 56.6, 116.1, 116.4, 122.6, 122.7, 144.9, 145.0, 156.7, 160.0, 167.1; MS(EI) 331(M^+); Anal. ($C_{19}H_{23}F_2N_3$·2HCl·0.5H_2O), C, H, N.

[3-(4-[3-phenylpropyl]-1-piperazinyl)propyl]-*N*,*N*-bis-(4-fluorophenyl)amine hydrobromide (**16**) was prepared as described for **11** from **15** (0.49 g, 1.48 mmol) and hydrocinnamic acid (0.37 g, 2.46 mmol). After coupling and reduction (0.67 g, 90%, from **15**), the amine was converted to the HBr salt in methanolic HBr and recrystallized from acetone/MeOH; mp 235−236 °C (dec); ^{1}H NMR δ 1.60−1.84 (4H,m), 2.17−2.65 (14H, m), 3.66 (2H, t, J = 7.0 Hz, $CH_2N(PhF)_2$), 6.9−7.3 (13H, m, aryl-Hs); ^{13}C NMR δ 25.1, 29.0, 34.1, 51.1, 53.6, 55.9, 58.4, 116.1, 116.4, 122.6, 122.7, 126.1, 128.7, 128.8, 142.5, 144.9, 156.7, 159.8, 168.0; MS(EI) 449(M^+) 218 ($^+CH_2N(PhF)_2$); Anal. ($C_{28}H_{33}F_2N_3$·2HBr), C, H, N.

[3-(4-Benzyl-1-piperazinyl)propyl]-*N*,*N*-bis(4-fluorophenyl)amine hydrobromide (**17**) was prepared as described for **12** from **15** (0.49 g, 1.48 mmol) and benzoyl chloride (0.29 mL, 2.50 mmol). After coupling and reduction (0.57 g, 91%, from **15**), the amine was converted to HBr salt and recrystallized from acetone/ether. mp 74−76 °C; ^{1}H NMR δ 1.76 (2H, m, J = 7.2 Hz, CH_2), 2.14−2.46 (10H, m), 3.51 (1H, s, NCH_2-aryl), 3.65 (2H, t, J = 7.2 Hz, $CH_2N(PhF)_2$), 7.25−7.32 (13H, m, aryl-Hs); ^{13}C NMR δ 15.6, 25.1, 25.7, 51.1, 53.5, 53.6, 55.9, 63.5, 116.1, 116.4, 122.6, 122.7, 127.4, 128.6, 129.6, 138.4, 144.9, 145.0, 156.7, 159.8; MS(EI) 421(M^+), 218 ($^+CH_2N(PhF)_2$); Anal. ($C_{26}H_{29}F_2N_3$·HBr·0.5H_2O), C, H, N.

[3-(4-[3-Hydroxy-3-phenylpropyl]-1-piperazinyl)propyl]-*N*,*N*-bis(4-fluorophenyl)amine Hydrobromide (19). A solution of **15** (750 mg, 2.27 mmol) in acetone (4.54 mL) was added to a stirred solution of 3-chloropropiophenone (556 mg, 3.30 mmol) in acetone (5.67 mL). The reaction was stirred overnight (12−18 h) at rt. After removing the solvent, the residue was extracted with $CHCl_3$ (3 × 100 mL) and aq NH_4-OH (20%, 100 mL), dried ($MgSO_4$), and concentrated. The crude ketone was purified by flash column chromatography (2% $CHCl_3$/MeOH/NH_4OH) to give the pure product as a yellow oil. The ketone **18** was reduced with LAH (0.131 g, 3.45 mmol) in THF to give the crude product which was converted to the HBr salt in methanolic HBr and was recrystallized from acetone (784 mg, 74%, from **15**); mp 184−185 °C; ^{1}H NMR δ 1.75−1.88 (4H, m), 2.17−2.74 (12H, m),3.67 (2H, t, J = 7.1 Hz, $CH_2N(PhF)_2$), 4.93 (1H, t, J = 5.5 Hz, CHO), 6.88−7.36 (13H, m, aryl-Hs); ^{13}C NMR δ 25.1, 34.0, 51.0, 53.6, 55.8, 57.4, 116.1, 116.4, 122.6, 122.7, 125.9, 127.3, 128.6, 144.9, 145.0, 145.2, 156.7, 160.0; Anal. ($C_{28}H_{33}F_2N_3O$·HBr), C, H, N.

Single-Crystal X-ray Diffraction Analysis of 11. $C_{30}H_{39}F_2N_3^{2+}$ 2$(Br)^-$ FW = 639.46, monoclinic space group $P2_1/c$, a = 14.997(1), b = 7.365(1), c = 28.823(1) Å, β = 105.089(1)°, V = 3073.8(1) Å^3, Z = 4, ρcalc = 1.382 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 3.623 mm^{-1}, F(000) = 1312, T = 293 K.

A colorless 0.20 × 0.12 × 0.06 mm crystal was used for data collection with a Bruker SMART[27] 6K CCD detector on a Platform goniometer. The Rigaku rotating Cu anode source was equipped with an incident beam Gobel mirrors. Lattice parameters were determined using SAINT[27] from 2706 reflec-

tions within $6.1 < 2\theta < 133.9°$. A set of 15678 reflections was collected in the ω scan mode. There were 5291 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELX-TL[28] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 varied 341 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms except the lower occupancy solvate atoms. H atoms were included using a riding model coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96 to 0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2 to 1.5 U_{eq}(C). Final residuals were $R1 = 0.032$ for the 4759 observed data with $F_o > 4\sigma(F_o)$ and 0.037 for all data. Final difference Fourier excursions of 0.20 and −0.22 eÅ^{-3}. The crystal was a merohedral monoclinic twin whose components were related by the twin matrix −1 0 0, 0 −1 0, 1 0 1. Tables of coordinates, bond distances and bond angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge, CB2 1EW, England.

Molecular Modeling Methods. Cross-validated comparative molecular field analysis (CoMFA) models of the binding domains on both DAT and σ_1 receptors were performed using Sybyl 6.7 (Tripos, Inc., St. Louis, MO) running on a Silicon graphics octane workstation and were constructed from the chemical fragments, DAT, and σ_1 receptor binding affinities of the rimcazole analogues shown in Tables 1 and 2. DAT and σ_1 receptor binding affinities for the previously described rimcazole analogues (**1**−**9**), the classical σ ligands rimcazole, *S*-(−)-3-PPP, PRE 084, carbetapentane and caramiphen, cocaine, and GBR 12909 are compared in Table 3 and these data were used in the molecular models as well.

All the compounds were built using the fragment library in Sybyl. The activity (K_i values) of these analogues varied from 8.5 to 174000 nM for DAT and 11.1−5720 nM for σ_1 receptors. The geometry's of the compounds were optimized using the conjugate gradient minimization with partial atomic charges derived from the Gasteiger−Marsilli method. The minimized structures were used as inputs for conformational searching using a systematic search routine on all rotatable bonds, wherein the bonds were rotated 360° in 15° increments. The conformational data from the X-ray structure of **11** (Figure 2) and other similar structures obtained from the Cambridge Structural Database (CSD) were used to compare and select the suitable torsions for the molecules. The CSD was searched for compounds containing *n*-propyl chains between a diarylamine and piperazine moiety and also for various N-substituents. The low energy conformers were aligned using the centroids of ring A and B and terminal nitrogen (Nb) of the piperazine ring (alignment I; see Figure 1) on the template compound **11**. Cocaine was not considered in deriving any alignment rules. However, for all other compounds, which lacked the second aromatic ring, the centroid of the aliphatic cyclic ring was used for superimposition on the template molecule.

Previous structure−activity relationships on super-potent σ_1 ligands has shown the importance of two hydrophobic interactions and an ionic interaction of the nitrogen atom.[21] Thus, to determine which of the two nitrogens in the piperazine ring is important, we derived another alignment (Alignment II), in which nitrogen (Na) was selected instead of the terminal nitrogen (Nb).

These aligned compounds were grouped and CoMFA interaction descriptors were derived from an sp^3 carbon atom with a van der Waals radius of 1.52 Å and a +1 charge. A default set of grid parameters was used. The 3D-QSAR models were obtained from the partial least squares (PLS) using the leave one out cross-validation technique. The optimum number of components was chosen based on the criteria where at least 5% increase in cross-validated r^2 was observed, with the use of each additional component. The final 3D-QSAR model was then derived from PLS analysis without cross-validation using the optimum number of components. The QSAR results were interpreted in the form of CoMFA contour plots, which were derived with default settings.

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